

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Giorgio Terenghi, Pari-Naz, Mohanna, and David P. Martin

Serial No.: 10/568,649

Art Unit: 1649

Filed: February 16, 2006

Examiner: Wang, Chang Yu

For: *POLYHYDROXYALKANOATE NERVE REGENERATION DEVICES*

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Commissioner for Patents
P.O. Box 1450
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SUBSTITUTE APPEAL BRIEF

Sir:

This is an appeal from the rejection of claims 1 and 3-6, and withdrawn claims 7-14, in the Office Action mailed on October 23, 2007, in the above-identified patent application. A Notice of Appeal was filed on February 25, 2008, with a Petition for Extension of Time for one month. The Commissioner is hereby authorized to charge \$255.00 the fee for filing an Appeal Brief, and the fee for a one month extension of time, for a small entity, to Deposit Account No. 50-3129.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTIES IN INTEREST

The real party in interest of this application is the assignee, Tepha, Inc.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 1, and 3-6 are pending, rejected, and on appeal. Claim 3 is objected to as depending on a cancelled claim. Claim 2 is cancelled. Claims 17-14 are pending and have been withdrawn from examination. Product claims 1 and 3-6 were elected with traverse on December 14, 2006, in response to a restriction requirement mailed on November 2, 2006. In an office action mailed on February 21, 2007, the Examiner acknowledged that the claims were related as product and process of use, and that withdrawn process claims 7-14 that recite all the limitations of the product claims would be rejoined upon allowance of the product claims. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment and Response filed on May 4, 2007. An amendment after final was filed on February 25, 2008. In the Advisory Action mailed March 13, 2008, the Examiner indicated that this amendment would not be entered, despite having previously indicated in an interview that the amendment would be entered. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit tube or sheet suitable for nerve repair, the pores in the conduit having a diameter of between five and 500 microns, wherein the polymer comprises 4-hydroxybutyrate (*see* page 6, lines 15-21). Dependent claim 3 specifies that the polymer is poly-4-hydroxybutyrate (*see* page 3, lines 18-21). Dependent claim 4 specifies that the pores of the conduits are greater than 5 μ m in diameter (*see* original claim 4 and page 5, lines 15-21). Dependent claim 5 specifies that the pores of the conduit are less than 500 μ m in diameter (*see* original claim 5 and page 5, lines 15-21). Dependent claim 6 specifies that the conduit comprises a material selected from the group consisting of nerve cells, growth factors, and drugs (*see* page 7, lines 1-8).

Withdrawn independent claim 7 defines a method for preparing a nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit tube or sheet wherein the polymer comprises 4-hydroxybutyrate and wherein the device is prepared by thermally induced phase separation of the polymer in a solvent in combination with salt particles, removing the polymer solvent, and removing the salt particles to form pores between five and five hundred microns in diameter (*see* page 6, lines 15-21). Claim 8 depends on claim 7 and specifies that the method comprises leaching with an alcohol followed by leaching with water or a solution comprising a surfactant (*see* from page 7, line 12 until page 8, line 31). Claim 9 depends on claim 7 and specifies that the device is prepared by a combination of thermally induced phase separation and poragen leaching (*see* page 6, lines 15-21 and original claim 9). Claim 10 depends on claim 8 and specifies the surfactant as a polysorbate (*see* page 8, lines 1-6 and original claim 10).

Withdrawn independent claim 11 defines a method of nerve repair or regeneration comprising providing a nerve regeneration device comprising 4-hydroxybutyrate polymer in the form of a wrapped porous conduit tube or sheet, the pores in the conduit having a diameter of between five and five hundred microns, wherein the diameter of the conduit is large enough so that it does not exert pressure on a regrowing nerve, but small enough to provide a good seal at the nerve (*see* page 6, lines 24 until page 7, line 1). Claim 11 depends on claim 12 and specifies that the method comprises inserting severed nerve ends into the conduit or wrapping the nerve ends with the polymer and sealing it into a conduit (*see* page 3, lines 24-27 and page 6, line 24 until page 7, line 1). Claim 13 depends on claim 12 and specifies that the device is sealed by application of heat (*see* page 3, lines 27-28 and original claim 13). Claim 14 depends on claim 11 and specifies that the method provides an axonal regeneration rate of at least 0.8 mm per day across a 10 mm sciatic nerve gap in an animal or human (*see* page 9, lines 1-31 and original claim 14).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are

- (i) whether claims 1 and 3-6 are obvious under 35 U.S.C. § 103(a) in view of International Application No. WO 01/54593 by Hadlock, et al. (“Hadlock”) in view of Martin, et al., *Biochem. Eng. J.* 16:97-105 (2003) (“Martin”).
- (ii) whether claims 1 and 3-6 are obvious under 35 U.S.C. § 103(a) in view of U.S. Patent No. 6,548,569 (“the ‘569 patent”) in view of U.S. Patent No. 5,584,885 to Seckel (“the ‘885 patent”) and evidentiary references Schlossauer, et al., *Neurosurgery*, 59:740-748 (2006) (“Schlossauer”) and Clavijo-Alvarez, et al., *Plast. Reconstr. Surg.*, 119:1839-51 (2007) (“Clavijo”).

(iii) whether claims 1 and 3-6 are obvious under 35 U.S.C. § 103(a) in view of U.S.

Patent No. 6,610,764 to Martin, et al. ("the '764 patent"), U.S. Patent No. 6,838,493 to Williams, et al. ("the '493 patent"), U.S. Patent No. 6,867,247 to Williams, et al. ("the '247 patent"), or U.S. Patent No. 7,179,883 to Williams, et al. ("the '883 patent") in view of the 885 patent and evidentiary references Schlossauer and Clavijo.

(iv) whether claims 1 and 3-6 are definite as required by 35 U.S.C. § 112 second paragraph.

(v) whether claims 1 and 3-6 are patentable under the judicially created doctrine of non-statutory double patenting in view claims 1-34 of the '764 patent, claims 1-4 and 6-28 of the '493 patent, claims 1-3 and 5-20 of the '569 patent, claims 1-4 and 6-30 of the '247 patent, claims 30 and 35-61 of the '883 patent", claims 1-18 and 21-25 of U.S. Published Application No. 2004/0234576 ("the '576 application), and claims 1-8 of U.S. Published Application No. 2006/0058470.

(7) ARGUMENTS

(A) The Claims

Nerve regeneration may occur if the end of the severed nerve is provided with a nerve growth guide. These are well known, as described in the background of the invention in appellants' application at pages 1-2. A number of materials have been used to form these nerve guides, the majority being non-biodegradable natural or synthetic polymers. As stated at page 2 of the application, several researchers have investigated the use of poly-3-hydroxybutrate (P3HB) as a material for nerve regeneration, and the use of growth factors and Schwann cells to prevent nerve cell death and promote regeneration. PCT WO 88/06866 to Aebischer *et al.* discloses tubular piezoelectric nerve conduits including a device formed from P3HB. Hazari *et*

al. in Vol. 24B *J. Hand Surgery*, pp. 291-295 (1999), Ljungberg *et al.* in Vol.19 *Microsurgery*, pp. 259-264 (1999), and Hazari *et al.* in Vol. 52 *British J. Hand Surgery*, pp. 653-657 (1999) also disclose P3HB conduits for nerve regeneration. PCT WO 03/041758 to Wiberg discloses a nerve repair unit comprising P3HB and an alginate matrix containing human Schwann cells, and PCT WO 01/54593 by Hadlock, *et al.* also discloses P3HB conduits that include Schwann cells. Hazari *et al.* in Vol. 52 *British J. Hand Surgery*, pp. 653-657 (1999), for example, discloses a rate of axonal regeneration using a P3HB conduit to bridge a 10 mm nerve gap in a rat sciatic nerve of approximately 10% at 7 days, 50% at 14 days, and complete regeneration at 30 days.

Appellants discovered, only upon testing, that P4HB polymeric nerve guides enhance the rate of nerve regrowth as compared to other polymeric nerve guides such as the P3HB nerve conduit described at page 2 of the present application. The evidence comparing the growth rate between the prior art P3HB nerve guides, as described in the literature, and P4HB nerve guides, is found in the examples of the application at example 5, pages 7-9.

As shown the data in example 5, in contrast to the P3HB nerve conduits, which achieved approximately 10% regeneration at 7 days (an axonal regeneration rate of 0.14 mm/day), by 10 days, PGP positive fibers were identified in the distal stump of all four P4HB conduits indicating that the 10 mm nerve gaps had been bridged. This indicates an axonal regeneration rate of at least 1 mm/day.

It is totally unexpected and non-obvious that by merely going from a P3HB to a P4HB nerve conduit, one could enhance the rate of regeneration from 0.14 mm/day to 1 mm/day.

(B) Rejection of claims 1 and 3-6 Under 35 U.S.C. § 103

The Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459 (1966). The *Graham* analysis was recently affirmed on April 30, 2007 by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

The obviousness analysis requires looking at the invention as a whole. "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

Hindsight analysis, such as picking and choosing from prior art references using the claimed invention as a template, has long been forbidden. *See e.g. In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988), stating "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." In *KSR*, the Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into the use

of hindsight” (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964)).

Analysis

(I) *Claims 1 and 3-6 are not obvious over International Application No. WO 01/54593 by Hadlock, et al. (“Hadlock” in view of Martin, et al., Biochem. Eng. J. 16:97-105 (2003).*

The scope and content of the prior art

Hadlock

Hadlock discloses a nerve regeneration conduit which includes a porous biocompatible support which is formed into a roll (Hadlock, page 1, lines 25-28). As described on page 2, lines 1-7, the support can be a synthetic polymer.

The polymers listed on page 2 are structurally and chemically distinct from P4HB polymers. In particular, the listed polymers are brittle, rigid, and not suitable for bending or rolling into a tube, in contrast to the elastic P4HB polymers.

Martin

Martin is a review article on poly-4-hydroxybutyrate (P4HB) describing some of the progress in the development of the polymer, its properties, uses and potential applications. Martin does not reference nerve guides. Examples of medical devices which can be prepared from the polymers include rods, bone screws, pins, surgical sutures, stents, tissue engineering devices, drug delivery devices, wound dressings, and patches such as hernial patches and pericardial patches. Martin does reference the use of fibrous meshes for tissue repair, in particular P4HB patches with pore sizes from 180-240 um were prepared for artery augmentation.

Differences between the prior art and the claims

The combination of Hadlock and Martin does not recite all of the limitations of the claims.

Neither of the Prior Art discloses the advantage of the P4HB for Nerve Regeneration

In combination, Hadlock teaches that the structure and chemical nature of the nerve guide is not critical. Martin does not disclose the advantages with respect to nerve regeneration of P4HB. Indeed, as noted above, the advantages were totally unexpected and apparent only after the studies were conducted. No one could have predicted this outcome. Accordingly, Hadlock and Martin cannot make obvious the claimed compositions.

Hadlock teaches away from the use of an elastic flexible polymer by defining polymers such as P3HB, PGA or PLGA, polycaprolactone, polyurethanes, and poly(organo)phosphazenes.

As stated by the Examiner in the office action mailed on October 23, 2007 (at page 7), Hadlock discloses porous nerve regeneration conduit comprising P3HB with a pore size between 10-100 μM and Martin discloses P4HB artery repair fibrous mesh patches with a pore size between 180-240 μM . The pore sizes disclosed in Martin are not for a nerve guide but for a fibrous mesh for tissue repair, and fall outside the range of the pore sizes desired in Hadlock for a nerve regeneration device. As stated in the MPEP §2145, "the claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose".

Martin teaches favorable properties of P4HB for use in a number of other types. ONCE one knows that they are desirable but the examiner has cited no art that such properties, instead of those relating to the polymers described by Hadlock, are desirable. Thus, there is no reason

why one of ordinary skill in the art would select P4HB (taught in Martin), for use as a nerve regeneration device from the disclosure in Hadlock.

No art has been cited that would lead one skilled in the art to have any expectation that the rate of growth of the nerves in the nerve conduit formed of a P4HB polymer would be faster, nor why.

It is well established, and the Court in *KSR* re-affirmed, that to be obvious, one must be able to predict with a reasonable degree of certainty that the combination of the prior art will have the claimed properties. One cannot use hindsight to arrive at this conclusion.

The Court also affirmed in *KSR* that evidence of unexpected results must be considered and that it is sufficient to rebut even a *prima facie* case of obviousness.

The Examiner alleged that Martin discloses that PHA polymers including poly 3-hydroxybutyrate (P3HB) and its copolymers are successful in use in peripheral nerve repair. According to the Examiner, this provides a motivation and an expectation of success in using P4HB in peripheral nerve regeneration since PHA polymers have been used to generate a nerve regeneration conduit. This conclusion is simply unsupported.

There are hundreds of PHA polymers. Appellants have selected a single class: P4HB polymers. There is no art that says that this one class, out of the multitude of other PHA polymers, would enhance nerve regeneration approximately **eight fold** as compared to the closest art, P3HB nerve conduits. Martin generally states that PHA polymers, including PHO and P3HB and its copolymers with other 3-hydroxyalkanoates, show promise in medical applications development, and specifically notes that P3HB is being evaluated for use in peripheral nerve repair. There is no disclosure or suggestion of the use of P4HB as a nerve conduit. There is no guidance in Martin to select P4HB with any expectation of success in

making a nerve conduit. The fact that Martin states that P4HB is more stable (than poly- α -hydroxy acid materials) and useful for tissue engineering does not imply that P4HB can be used for any and every device, and one of ordinary skill in the art would not conclude as such. There are over 100 different PHAs and a disclosure that one of these (P3HB) has been used in peripheral nerve repair does not make obvious selecting P4HB from the group. Numerous PHA's share the same stability over poly- α -hydroxy acid materials and have been disclosed as useful in tissue engineering. There is no direction to select P4HB with any expectation of success. Furthermore, the Examiner's allegation that Martin discloses P4HB for use in tissue regeneration including nerve regeneration is incorrect. Martin is clear about which tissues have been regenerated using P4HB (see Martin, page 97, under "Introduction"). Nerves are not included in the list.

The Examiner also alleged that use of P4HB to substitute P3HB to make or improve the nerve conduits of Hadlock would be obvious because the results of nerve regeneration using a conduit of P3HB is known, and the results of substituting P3HB with P4HB are also expected because Hadlock teaches a nerve regeneration conduit comprising biodegradable polymers of PHA. Appellants respectfully disagree. As noted above, one of ordinary skill in the art knows that there are over 100 polymers of PHA, and not all PHAs will be suitable for making nerve guides. Some PHA's are elastomeric and would collapse on the regenerating nerve, others are too stiff and would be difficult to manipulate. So, absent some guidance, there would be no reason to select P4HB from the over 100 available PHA's. There is no evidence that any and every PHA will be suitable for nerve guides.

Moreover, and more importantly, there is no way anyone skilled in the art could predict that if P4HB were selected from the large class of PHAs, that it could enhance the rate of regeneration from

In summary, the prior art does not teach the selection of an elastic, flexible polymer, a P4HB polymer, instead of a brittle or rigid polymer, such as P3HB or the polymers disclosed by Hadlock. The prior art also does not teach that the selection of polymer alters the rate of regeneration, much less that the selection of a P4HB polymer can be used to enhance the rate of regeneration from a rate of 1 mm in 7 days (i.e., 10% of a 10 mm gap) to completely closed, 10 mm in 10 days (i.e., 100% of a 10 mm gap). This is a huge difference.

(II) Claims 1 and 3-6 are not obvious over a combination of 'the 569 patent or the '764 patent, the '493 patent, the '247 patent and the '883 patent and Seckel.

The scope and content of the prior art

The '569 patent, the '764 patent, the '493 patent, the '247 patent and the '883 patent (jointly referred to herein as "the Metabolix patents") all share the same specification, thus, discussion regarding these patents will be based on the '569 patent.

The Metabolix patents

The '569 patent discloses PHA compositions that can be used in both new and existing medical application devices formed of or including biocompatible polyhydroxyalkanoates that have controlled degradation rates (*see abstract*). The '569 patent discloses additives that can be used to alter the **degradation rates** of the PHA formulations, such as inorganic acids, additives that form pores, modification of pendant groups or incorporation into the polymer backbone chemical linkages which are more susceptible to hydrolysis or enzymatic attack (from col. 10, line 6 until col. 12, line 15).

There is no disclosure of porosity for regrowth of nerves, no disclosure of chemical compositions for formation of sheets that can be rolled to form tubes or which are elastic and flexible enough to serve as nerve conduits. There is no disclosure of selecting a specific chemical composition to alter the rate of neural regeneration. There is no disclosure that P4HB is particularly useful for nerve regeneration as compared to any of the other hundreds of PHAs.

It is clear the only way this disclosure can be interpreted to make obvious the claimed subject matter is by using hindsight. This has been repeatedly refuted as appropriate, however - the references must make obvious the claimed subject matter, not Appellants' own disclosure.

Seckel

Seckel discloses a regeneration chamber for promoting and controlling the growth of biological tissue. The regeneration chamber includes a chamber enclosing and defining a volume in which biological tissues are to be grown, an input port for injecting agents for promoting and controlling the growth of the biological tissues into the chamber, and an output port for pressure release and for removing agents and byproducts (col. 3, lines 55-65). The materials that can be used to make these devices are listed at col. 8, lines 12-28. These apparently can be degradable or non-degradable, polymer or non-polymer, tissue or synthetic, "cells" and apparently anything else known to mankind. It is not clear how a number of these materials could be used, but what is clear is that the biodegradable polymers that are listed are not flexible or elastic nor do they have pores nor do they have any means of enhancing the rate of nerve regeneration.

The majority of these materials correspond to those that have been identified as having "significant shortcomings" - see page 2, lines 5-15, and reference cited therein.

Differences between the prior art and the claims

A combination of the Metabolix patents and Seckel does not yield the claimed nerve regeneration device. Neither the Metabolix patents nor Seckel discloses a nerve regeneration device formed of a P4HB polymer, with the recited pore size range. The Metabolix patents discloses that the rate of polymer degradation (not nerve regeneration) of the devices may be enhanced by additives which form pores and that the diameter of the pore-forming particles may be between nanometers and 500 microns i.e. the range of the pore size is from greater than 0.001 microns to 500 microns. There is no disclosure to select from within this wide pore range to arrive at the narrower pore range of 5-500 microns recited in the claims or any expectation that there would be benefits associated with such a pore size selection with respect to nerve regeneration. As stated in the MPEP §2144 "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus".

Appellants respectfully disagree with the Examiner's allegation that the Metabolix patents shows conduits having both a large range and a narrow range or pore sizes. The '569 patent discloses the diameter of the particles that can be used to form pores as between nanometers and 500 microns and shows an example of how to create such pores using sodium chloride crystals between 80 and 180 μm . This is not tantamount to a disclosure of a nerve regeneration device having a pore size between 80 and 180 μm , nor is there any teaching leading one skilled in the art to such a device or method of manufacture. Appellants are not claiming creating pores in a polymeric material. The '569 patent discloses a wide pore range that is relevant to enhancing polymer **degradation**; not that relates to nerve regeneration. The present application discloses a combination of polymer selection and relevant pore size for the claimed

device, that provides unexpected nerve regeneration (discussed below). Thus, the '569 patent considered as a whole teaches ways to alter rates of degradation; not methods to improve rates of nerve regeneration. No reason is provided for why one of ordinary skill in the art would, from the list of additives (i.e. additives having acidic or basic pH such as inorganic acids, organic acids, organic bases, surfactants, acidic nucleophiles, basic nucleophiles, acidic electrophiles; pore forming agents such as gelatin, agarose, volatile salts and starches; or hydrophobic coatings such as phospholipids or cholesterol) disclosed for us in altering the degradation rate of devices made of PHA polymers, specifically select pore forming agents and then additionally select a pore size of 5 - 500 microns from the range of nanometer-500 micron pore size disclosed in 'the 569 patent for use in making a chemical composition to alter the rate of neural regeneration. What is relevant in the '469 patent is the percentage porosity (see Example 4), not the pore size, with devices that are 80% more porous degrading faster-thus, according to the disclosure in the '569 patent, a device with a pore size range of 0.002-0.9 microns, for example, would be expected to show enhanced degradation so long as it is 80% porous.

The Examiner has provided no reason why one of ordinary skill in the art would select from the general disclosure in the '569 patent (1) P4HB polymer; (2) flexible material; (3) defined pore size; and have any expectation of improving nerve regeneration over the levels shown in the prior art. This is not obvious from any prior art combination.

With respect to the Examiner's evidentiary references (Schlossauer and Clavijo), Appellants are unclear as to how the Examiner arrived at the conclusion that these references disclose that NEUROTUBE™ has a pore size of 30-50 μm , nor its relevance to what is claimed. Clavijo discloses nerve guides made by incorporating Cultispheres within polycaprolactone (CultiGuides) and compares their CultiGuides with Neurotubes (see Clavijo, page 1840,

paragraph bridging left and right columns and second paragraph right col.). Under Materials and Methods, Clavijo discloses their nerve guide fabrication, which they made porous by incorporation of sodium chloride crystals 30-50 μm in diameter. This disclosure is not about the NEUROTUBETM, it is about the CultiGuide disclosed in Clavijo; Clavijo is not prior art to this application. Schlossauer does not mention a pore size range.

Significantly, the articles describe devices formed of polycaprolactone, which is a very brittle polymer. Even after Appellants' filing date, there was still no recognition in the field that one could use a flexible, degradation porous polymer which would be suitable for nerve regeneration **and** enhance the rate of nerve regeneration.

(III) Evidence of Secondary considerations

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, unexpected results, etc.

Various materials such as silicone rubber, polyglactin mesh, acrylic copolymer tubes and other polyesters have been tested as candidates for nerve channel conduits. These however have been reported to include several significant shortcomings (*see* the present specification at least at page 2, lines 5-10). Several researches have investigated the use of poly-3-hydroxybutyrate (P3HB) in a bid to improve upon these results with positive results. However the rate of nerve regeneration obtained with P3HB is inferior when compared to the results obtained with a nerve graft. By combining the polymer and pore size range selection recited in claim 1, the present claims provide a nerve regeneration device with which unexpected nerve regeneration (1mm/day) is obtained when compared to 0.14 mm/day (i.e.10% of 10mm/7days) for example, using P3HB (*see* Hazari, et al. *Br. J. Hand Surg.*, 653-57 (1999) (Submitted with the Information Disclosure Statement filed on August 30, 2006 and considered by the Examiner on February 2,

2007). Thus, the claims provide a nerve regeneration device which has a superior rate of axonal regeneration. The claimed device also meets the long felt but unmet need for a nerve regeneration device which obtains axonal regeneration that is comparable to that obtained using a nerve graft (*see* the present specification at least at page 3, lines 3-10).

(IV) Conclusion

Even if the examiner has made a *prima facie* case of obviousness (which is believed not to be the case, the unexpected results rebut this. This evidence shifts the burden back to the examiner to establish why the prior art makes obvious the claimed subject matter, using objective evidence, not mere argument.

As stated above, the claims are drawn to a flexible P4HB nerve regeneration device which has a superior rate of axonal regeneration when compared with the axonal generation in the prior art. The MPEP (§2144.05) states “Appellants can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing “(1) [t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art.” *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004)”.

Thus, at least for the reasons discussed above, claims 1 and 3-6 are non obvious over the cited art.

(C) Rejection Under 35 U.S.C. § 112

Claims 1 and 3-6 were rejected under 35 U.S.C. §112 second paragraph as indefinite. According to the Examiner, the term “suitable” in the claims is relative, rendering the claims indefinite. Appellants respectfully disagree. One of ordinary skill in the art would understand the word suitable as used in claim 1. The word suitable means “meant or adapted for an

occasion or use". One of ordinary skill in the art knows how to adapt a sheet or tube for nerve repair. Therefore, claims 1 and 3-6 are definite.

(D) Rejection of claims 1 and 3-6 under the judicially created doctrine of obviousness type double patenting.

Legal Standard

Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent. *In re Van Ornum*, 214 U.S.P.Q. 761 (C.C.P.A.1982); *In re Zickendraht*, 138 U.S.P.Q. 22 (C.C.P.A. 1963). As discussed below, this situation can only arise if there is common ownership.

The patent rules make clear the necessity for common ownership; and the MPEP affirms this requirement.

37 C.F.R. § 1.321(c)(3) requires that "a terminal disclaimer filed to obviate a judicially created double patenting rejection in a patent application... must...include a provision that any patent granted on that application...shall be enforceable only for and during such period that said patent is **commonly owned** with the application or patent which formed the basis for the rejection." (emphasis added).

37 C.F.R. 1.78(c) provides "If an application or a patent under reexamination and at least one other application naming different inventors are owned by the same person and contain conflicting claims, and [...] if the claimed inventions were **commonly owned**, or subject to an obligation of assignment to the same person, at the time the later invention was made, the conflicting claims may be rejected under the doctrine of double patenting in view of such commonly owned or assigned applications or patents under reexamination." (emphasis added).

There is only one exception to the requirement for common ownership, **where there is a joint research agreement, which is not applicable here.** In describing the analysis that an Examiner must conduct to determine if an obviousness-type double patenting rejection is proper, the MPEP explains:

Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a **commonly owned patent, or a non-commonly owned patent but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3),** when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent.
M.P.E.P 804 (II)(B)(1) (emphasis added).

The M.P.E.P elaborates on the common ownership requirement in section 804.03. In this section, the M.P.E.P notes that “[c]laims in commonly owned applications of different inventive entities may be rejected on the ground of double patenting.” The M.P.E.P. continues by referring to only one situation in which non-commonly owned applications or an application and a granted patent may be rejected under obviousness-type double patenting. This situation is when the claims define inventions resulting from activities undertaken within the scope of a joint research agreement. The M.P.E.P. states “Claims may also be rejected on the grounds of nonstatutory double patenting in certain **non-commonly owned applications that claim inventions resulting from activities undertaken with the scope of a joint research agreement as defined in 35 U.S.C. 103(c)(3).**” (emphasis added).

The M.P.E.P. provides further guidance to Examiners regarding when to make a double patenting rejection. The M.P.E.P. explains that when the facts support both rejections, “both a double patenting rejection **based on common ownership** and a rejection based on 35 U.S.C.

102(e)/ 103 prior art” should be made by the Examiner. M.P.E.P §804.03(II)(C) (emphasis added) However, if there is no common ownership, the M.P.E.P. does not instruct the Examiner to make a double patenting rejection. Rather, the M.P.E.P. notes that only a rejection under 35 U.S.C. 102(e)/ 103 prior art should be made first. “Until appellant has established that a reference is disqualified as prior art under the joint research agreement exclusion of 35 U.S.C. 103(c), the examiner should NOT apply a double patenting rejection based on a joint research agreement.” M.P.E.P §804.03(II)(C) (emphasis in original).

Accordingly, it is clear that this rejection is legally improper with respect to U.S. Patent Nos. 6,610,764; 6,838,493; 6,548,569; 6,867,247; and 7,179,883 which do not share common ownership with the present application. Thus, the only possible rejection in view of U.S. Patent Nos. 6,610,764; 6,838,493; 6,548,569; 6,867,247; and 7,179,883 could have been made under 35 U.S.C. §102 and/or §103. The 103 rejection has been made and is addressed above.

The claims are novel under 102 and inventive under 103 in view of U.S. Patent Nos. 6,610,764; 6,838,493; 6,548,569; 6,867,247; and 7,179,883. Discussion regarding the disclosure of U.S. Patent Nos. 6,838,493; 6,548,569; 6,867,247; and 7,179,883 with respect to 35 U.S.C. §102 and/or §103 will be grouped together since they all share the same specification. U.S. Patent No. 7,179,883 is a continuation of allowed prior application U.S. Serial. No. 10/136,449, now U.S. Patent No. 6,867,247 which is a divisional of U.S. Ser. No. 09/535,146, now U.S. Patent No. 6,548,569. U.S. Patent No. 6,548,569 is a divisional of prior application U.S. Ser. No. 09/535,146, now U.S. Patent No. 6,548,569. None of the claims in any of these patents relate to selection of P4HB as compared to any other PHA for use in nerve regeneration. Only the ‘493 patent even mentions nerve guide in a claim, in which it is listed with many other devices, and a long list of possible PHAs for use in manufacture thereof.

(I) Non Statutory double patenting rejection over U.S. Patent Nos. 6,610,764; 6,838,493; 6,548,569; 6,867,247; and 7,179,883 owned by Metabolix, Inc.

(a) U.S. Patent No. 6,610,764 to Martin, et al. ("the '764 patent")

Claims 1 and 3-6 were rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view claims 1-34 of U.S. Patent No. 6,610,764 ("the '764 patent"). Appellants respectfully traverse this rejection for at least the reasons set forth below.

(i) The Rejection is legally improper

There is no common ownership

The '764 patent is owned by Metabolix, Inc. The pending application is owned by Tepha, Inc. Thus the '764 patent and the pending application are not commonly owned. Additionally, the claims in the '764 patent and the claims in the pending application are not the result of research that was the subject to a joint research agreement. Therefore the rejection for obviousness-type double patenting over claims 1-34 of the '764 patent is a legally improper rejection.

Even if the rejection was a proper rejection, the present claims are patentably distinct from claims 1-34 of the '764 patent as shown by the claim-by-claim analysis below.

(ii) Claims 1 and 3-6 are not obvious in view of claims 1-34 of the '764 patent

The scope of claims 1-34 of the '764 patent

Independent claim 1 defines a biocompatible polyhydroxyalkanoate composition that has a controlled degradation rate of less than one year by hydrolysis in vivo, selected from the group consisting of polyhydroxyalkanoate compositions wherein monomeric units are incorporated as

chemical linkages into the polymer backbone which alter the chemical stability of the polymer, wherein linkages are incorporated into the polymer backbone which alter the chemical stability of the polymer, and wherein pendant groups are incorporated into the polymer which alter the chemical stability of the polymer, wherein the polyhydroxyalkanoate has a weight-average molecular weight in the range between 10,000 to 10,000,000 Dalton. Claims 2-11, 21-28 and 30-34 depend directly from claim 1. Claims 21-23 specify that the compositions comprise pore forming agents

Independent claim 12 defines a biocompatible polyhydroxyalkanoate composition that has a controlled degradation rate of less than one year by hydrolysis in vivo, selected from the group consisting of polyhydroxyalkanoate compositions, wherein monomeric units are incorporated as chemical linkages into the polymer backbone which alter the chemical stability of the polymer and contain more than two functional groups selected from the group consisting of reactive groups which can cleave the polymer backbone by an intramolecular or intermolecular reaction, acidic or basic groups, and units that modulate the reactivity of the ester linkage selected from the group consisting of 2-hydroxyacids, 2-hydroxyethoxy acetic acid, 2-hydroxypropoxy acetic acid, amino acids, amino alcohols, and diacids, which are positioned within the polymer backbone to increase the rate of degradation, triols, and tetraols, wherein linkages are incorporated into the polymer backbone which alter the chemical stability of the polymer, wherein pendant groups are incorporated into the polymer which alter the chemical stability of the polymer, and wherein the polyhydroxyalkanoate has a weight-average molecular weight in the range between 10,000 to 10,000,000 Dalton. Claim 29 depends on claim 12

Differences between claims 1-34 of the '764 patent and claims 1 and 3-6 of the present application.

Claims 1-34 of the '764 patent do not relate to nerve regeneration devices; do not lead one to make a flexible porous nerve regeneration device; do not teach one of ordinary skill in the art that porosity or polymer composition would have any impact on nerve regeneration, and therefore do not make obvious the claims of this application.

For at least the reasons discussed in the claim-by-claim analysis above, claims 1 and 3-6 of the present application are non-obvious in view of claims 1-34 of the '764 patent. As explained above, the claims in the present application could only be rejected under 35 U.S.C. §102 and/or §103. However, the '764 patent does not anticipate or make obvious the claims of the present application for at least the reasons set forth below.

(iii) Even if a rejection under 35 U.S.C. §102 and/or §103 had been made, the claims are not anticipated or made obvious by the '764 Patent

The '764 patent discloses polyhydroxyalkanoate compositions with controlled degradation rates.

The '764 patent does not disclosed the claimed composition for nerve regeneration, which comprises P4HB and the pore sizes recited in the claims. Therefore, the '764 patent does not anticipate the claims.

The '764 patent does not recite all of the claim limitations as is required by a rejection under 35 U.S.C. §103(a). The '764 patent discloses as one of the additives which alter the degradation rates of polymers, pore forming agents, discloses that the diameters of the particles may suitably be between nanometers and 500 microns. There is nothing in the '764 patent that would lead one of ordinary skill in the art to select poly 4HB and then the pore size range recited

in the claims, for a nerve regeneration device, nor would one of ordinary skill in the art expect that by combining the polymer and pore size range selection recited in claim 1 of the present application, a nerve regeneration device can be obtained with the unexpectedly superior nerve regeneration (1mm/day) when compared to 0.14mm/day (i.e. 1mm/7 days) for example, using P3HB. For at least the reasons set forth above, the '764 patent does not make the claims obvious.

b) U.S. Patent No. 6,838,493 to Williams, et al. ("the '493 patent")

Claims 1 and 3-6 were rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view claims 1-4 and 6-28 of U.S. Patent No. 6,838,493 ("the '493 patent"). Appellants respectfully traverse this rejection for at least the reasons set forth below.

(i) The Rejection is legally improper

There is no common ownership

The '493 patent is owned by Metabolix, Inc. The pending application is owned by Tepha, Inc. Thus the '493 patent and the pending application are not commonly owned. Additionally, the claims in the '493 patent and the claims in the pending application are not the result of research that was the subject to a joint research agreement. Therefore the rejection for obviousness-type double patenting over claims 1-4 and 6-28 of the '493 patent is a legally improper rejection.

Even if the rejection was a proper rejection, the present claims are patentably distinct from claims 1-4 and 6-28 of the '493 patent as shown by the claim-by-claim analysis below.

(ii) Claims 1 and 3-6 are not obvious in view of claims 1-4 and 6-28 of the '493 patent

The scope of claims 1-4 and 6-28 of the '493 patent

Claims 1-4 and 6-28 of the '493 patent define a device comprising a biodegradable polyhydroxyalkanoate polymer composition that has a controlled degradation rate, under physiological conditions, wherein the average molecular mass loss of the polymer decreases 20% to 50% over a ten week time period in vivo or wherein the percent mass loss is greater than 5% over a six week period in vivo, wherein the degradation rate of the polyhydroxyalkanoate polymer is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the polyhydroxyalkanoate polymer has a weight average molecular weight of between 10,000 and 10,000,000 Daltons, and wherein the device is selected from the group consisting of sutures, suture fasteners, meniscus repair devices, rivets, tacks, staples, screws, bone plates and bone plating systems, surgical mesh, repair patches, slings, cardiovascular patches, orthopedic pins, adhesion barriers, stents, guided tissue repair/regeneration devices, articular cartilage repair devices, nerve guides, tendon repair devices, atrial septal defect repair devices, pericardial patches, bulking and filling agents, vein valves, bone marrow scaffolds, meniscus regeneration devices, ligament and tendon grafts, ocular cell implants, spinal fusion cages, skin substitutes, dural substitutes, bone graft substitutes, bone dowels, wound dressings, and hemostats.

Differences between claims 1-4 and 6-28 of the '493 patent and claims 1 and 3-6 of the present application.

Claims 1-4 and 6-28 of the '493 patent relate to rate of degradation of PHA's in general; not nerve regeneration devices that have an enhanced rate of regeneration. One skilled in the art

would be more likely to look at polymers having a particular rate of degradation and not at the rate of nerve regeneration.

(c) U.S. Patent No. 6,548,569 to Williams, et al. ("the '569 patent")

Claims 1 and 3-6 were rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view claims 1-3 and 5-20 of U.S. Patent No. 6,548,569 ("the '569 patent"). Appellants respectfully traverse this rejection for at least the reasons set forth below.

(i) The Rejection is legally improper

There is no common ownership

The '569 patent is owned by Metabolix, Inc. The pending application is owned by Tepha, Inc. Thus the '569 patent and the pending application are not commonly owned. Additionally, the claims in the '569 patent and the claims in the pending application are not the result of research that was the subject to a joint research agreement. Therefore the rejection for obviousness-type double patenting over claims 1-3 and 5-20 of the '569 patent is a legally improper rejection.

Even if the rejection was a proper rejection, the present claims are patentably distinct from claims 1-3 and 4-20 of the '569 patent as shown by the claim-by-claim analysis below.

(ii) Claims 1 and 3-6 are not obvious in view of claims 1-3 and 5-20 of the '569 patent

The scope of claims 1-3 and 5-20 of the '569 patent

Claims 1-3 and 5-20 of the '569 patent define a biodegradable polyhydroxyalkanoate composition comprising a polyhydroxyalkanoate polymer having a controlled degradation rate of less than one year in vivo, under physiological conditions, wherein the degradation rate of the polyhydroxyalkanoate polymer is manipulated through addition of components to the polymeric

composition, selection of the chemical composition of the polyhydroxyalkanoate polymer through selection of monomeric units, as chemical linkages, which are incorporated into the polymer, by alteration of the linkages, chemical backbone or pendant groups, molecular weight, processing conditions, or form of the composition, and wherein the polyhydroxyalkanoate polymer has a weight average molecular weight of between 10,000 and 10,000,000 Dalton; and wherein the form of the composition refers to the porosity and surface area of the composition.

Differences between claims 1-3 and 5-20 of the '569 patent and claims 1 and 3-6 of the present application.

Similar to the claims in the '493 patent, Claims 1-3 and 5-20 of the '569 patent relate to rate of degradation of PHA's in general; not nerve regeneration devices that have an enhanced rate of regeneration. One skilled in the art would be more likely to look at polymers having a particular rate of degradation and not at the rate of nerve regeneration.

(d) U.S. Patent No. 6,867,247 to Williams, et al. ("the '247 patent")

Claims 1 and 3-6 were rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view claims 1-4 and 6-30 of U.S. Patent No. 6,867,247 ("the '247 patent"). Appellants respectfully traverse this rejection for at least the reasons set forth below.

(i) The Rejection is legally improper

There is no common ownership

The '247 patent is owned by Metabolix, Inc. The pending application is owned by Tepha, Inc. Thus the '247 patent and the pending application are not commonly owned. Additionally, the claims in the '247 patent and the claims in the pending application are not the result of research that was the subject to a joint research agreement. Therefore the rejection for

obviousness-type double patenting over claims 1-4 and 6-30 of the '247 patent is a legally improper rejection.

Even if the rejection was a proper rejection, the present claims are patentably distinct from claims 1-4 and 6-30 of the '247 patent as shown by the claim-by-claim analysis below.

(ii) Claims 1 and 3-6 are not obvious in view of claims 1-4 and 6-30 of the '247 patent

The scope of claims 1-4 and 6-30 of the '247 patent

Claims 1-4 and 6-30 of the '247 patent define a method of enhancing the healing of a wound, injury, or defect in a site in a patient, comprising administering at the site a device comprising a biocompatible polyhydroxyalkanoate composition wherein the degradation rates of the polyhydroxyalkanoates is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the mass loss of the polyhydroxyalkanoate, as measured by gas chromatography, is greater than 5% over a six week period *in vivo*, or wherein the average molecular mass of the polyhydroxyalkanoate, as measured by gel permeation chromatography, decreases 20% to 50% over a ten week period *in vivo*, and wherein the device is selected from the group consisting of sutures, suture fasteners, meniscus repair devices, rivets, tacks, staples, screws, bone plates and bone plating systems, surgical mesh, repair patches, slings, cardiovascular patches, orthopedic pins, adhesion barriers, stents, guided tissue repair/regeneration devices, articular cartilage repair devices, nerve guides, tendon repair devices, atrial septal defect repair devices, pericardial patches, bulking and filling agents, ligament and tendon grafts, ocular cell implants, spinal fusion cages, heart valves, vascular grafts, skin substitutes, dural substitutes, bone graft substitutes, bone dowels, wound dressings, and hemostats.

Differences between claims 1-4 and 6-20 of the '247 patent and claims 1 and 3-6 of the present application.

The claims in this patent also focus on PHAs having controlled degradation rates, not flexibility and porosity for a nerve regeneration device which provides an enhanced rate of degradation. There is nothing in the claims cited by the Examiner that would lead one of ordinary skill in the art to select poly 4HB over any other polyhydroxyalkanoates and the recited pore sizes in claims 1 and 3-6 of the present application, with any expectation of the superior nerve regeneration obtained with a combination selected polymer and pore size.

(e) U.S. Patent No. 7,179,883 to Williams, et al. ("the '883 patent")

Claims 1 and 3-6 were rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view of claims 30 and 35-61 of U.S. Patent No. 7,179,883 ("the '883 patent"). Appellants respectfully traverse this rejection for at least the reasons set forth below.

(i) The Rejection is legally improper

There is no common ownership

The '883 patent is owned by Metabolix, Inc. The pending application is owned by Tepha, Inc. Thus the '883 patent and the pending application are not commonly owned. Additionally, the claims in the '883 patent and the claims in the pending application are not the result of research that was the subject to a joint research agreement. Therefore the rejection for obviousness-type double patenting over claims 30 and 35-61 of the '883 patent is a legally improper rejection.

Even if the rejection was a proper rejection, the present claims are patentably distinct from claims 30 and 35-61 of the '883 patent as shown by the claim-by-claim analysis below.

(ii) Claims 1 and 3-6 are not obvious in view of claims 30 and 35-61 of the '883 patent

The scope of claims 30 and 35-61 of the '883 patent

Appellants are unclear as to which claims the Examiner is referring to, since the '883 patent does not have claims 36-61. Thus, Appellants will discuss all of the claims in the '883 patent.

Claims 1 and 5-30 of the '883 patent define a device comprising a biodegradable polyhydroxyalkanoate polymer composition that has a controlled degradation rate of less than one year, under physiological conditions, wherein the degradation rate of the composition is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the device is selected from the group consisting of rotator cuff repair devices, temporary wound support devices, bladder patches, pledgets, soft tissue reinforcement devices, vascular patches, devices for atrial wall repair, bone marrow scaffolds, ligament repair devices, rods, washers, screws, pins, struts, plates, and staples used in spinal fusion cages, stents, sewing rings, stiffeners used in heart valve supports, cell encapsulation devices, coated devices, defect filling devices, organ patches, organ salvage devices, staple line reinforcement devices, pelvic floor reconstruction devices, devices for closure of ventricular septal defects, drug delivery devices, devices for delivery of biological factors, and devices comprising encapsulated proteins, antibodies, enzymes, peptides, polysaccharides, saccharides, organic drugs, inorganic drugs, nucleic acids, antigens, inhibitors, clot dissolving agents, hormones, nucleic acid, and/or lipids.

Claims 2-4 define a method of making the device defined by claim 1.

The differences between claims cited by the Examiner and claims 1 and 3-6 of the present application.

None of the claims cited by the Examiner define a nerve regeneration device in the form of a porous conduit with pores having a diameter of between 5 and 500 microns as recited in claims 1 and 3-6 of the present application.

Moreover, there is nothing in any of the claims that would lead one of ordinary skill in the art to select the pore sizes recited in the claims.

The Examiner admitted that the prior art claims do not specify a conduit as claimed, with pore size between 5-500 microns. However, according to the Examiner, the specification teaches a process of generation of a conduit with a pore size between nanometers-500 μm . Appellants respectfully draw the Examiner's attention to the fact that the claims, not the specification, should be analyzed (*see* MPEP §§ 800-822). As admitted by the Examiner, the claims do not specify a conduit with the claimed pore sizes. Furthermore, there is nothing in any of the claims cited by the that would direct one of ordinary skill in the art to modify the claims to arrive at the recited pore sizes.

(f) Even if a rejection under 35 U.S.C. §102 and/or §103 had been made, the claims are not anticipated or made obvious by U.S. Patent No. 6,838,493; 6,548,569; 6,867,247; and 7,179,883 (“the Metabolix Patents”)

None of the Metabolix Patents disclose the claimed nerve conduit. Therefore, none of the patents anticipate the claims.

Furthermore, none of the Metabolix Patents make the claims obvious. The Metabolix Patents disclose PHA compositions that can be used in both new and existing medical application devices formed of or including biocompatible polyhydroxyalkanoates that have

controlled degradation rates (*see* abstract of the '569 patent for example). The Metabolix Patents disclose additives that can be used to alter the **degradation rates** of the PHA formulations, such as inorganic acids, additives that form pores, modification of pendant groups or incorporation into the polymer backbone chemical linkages which are more susceptible to hydrolysis or enzymatic attack (from col. 10, line 6 until col. 12, line 15 of the '569 patent).

There is no disclosure of porosity for regrowth of nerves, no disclosure of chemical compositions for formation of sheets that can be rolled to form tubes or which are elastic and flexible enough to serve as nerve conduits. There is no disclosure of selecting a specific chemical composition to alter the rate of neural regeneration. As stated above in response to the 103 rejection, no reason is provided for why one of ordinary skill in the art would select pore forming agents from the list of additive disclosed in the Metabolix Patents and additionally select a pore size of 5 - 500 microns from the range of nanometer-500micron pore size disclosed in the Metabolix Patents (both of which are disclosed as relevant for altering the rate of degradation device), and use the combination (i.e. P4HB with 5-500 micron pore size) for neural regeneration.

It is clear the only way this disclosure can be interpreted to make obvious the claimed subject matter is by using hindsight. This has been repeatedly refuted as appropriate, however - the references must make obvious the claimed subject matter, not Appellants' own disclosure.

(g) Evidence of Secondary considerations

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, unexpected results, etc.

As stated above in response to the rejection of the claims as obvious under 35 U.S.C. § 103(a), by combining the polymer and pore size range selection recited in claim 1, the present

claims provide a nerve regeneration device with which unexpected nerve regeneration (1mm/day) is obtained when compared to 0.14mm/day (i.e. 1mm/7days) for example, using P3HB and meets the long felt but unmet need for a nerve regeneration device which obtains axonal regeneration that is comparable to that obtained using a nerve graft (*see* the present specification at least at page 3, lines 3-10).

For at least the reasons set forth above, claims 1 and 3-6 of the present application are nonobvious over the cited claims and over the disclosure of the Metabolix Patents.

(II) Non Statutory double patenting rejections in view of U.S. Published Application Nos. 2004/0234576 ("the '576 application), and 2006/0058470 ("the '470 application) owned by Tepha, Inc..

The '576 and the '470 applications are commonly owned with the present application; thus a double patenting rejection may be appropriate. However, Appellants respectfully traverse this rejection because the claims in the '576 and the '470 applications are not obvious variants of the present claims.

(a) U.S. Published Application No. 2004/0234576 (U.S. Serial No. 10/835,926)

Claims 1 and 3-6 of the present application were provisionally rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view of claims 1-18 and 21-25 of U.S. Published Application No. 2004/0234576. Appellants note that this is a provisional rejection. Claims 1-18 and 21-25 of the '576 application have been cancelled. Therefore, this rejection is moot.

(b) U.S. Published Application No. 2006/0058470 (U.S. Serial No. 11/193,580)

Claims 1 and 3-6 of the present application were provisionally rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view of claims 1-8 of

U.S. Published Application No. 2006/0058470. Appellants note that this is a provisional rejection. Claims 1-8 are no longer under Examination in the '470 application. In a response to a Restriction Requirement requiring election between claims 9-16 and claims 1-8, of the '476 application, claims 9-16 were elected for prosecution, without traverse. Therefore, the rejection of claims 1 and 3-6 as obvious in view of claims 1-8 of the '470 application is moot.

CONCLUSION

The claims are not anticipated by or obvious over the prior art due to differences between the claimed elements and the unexpected results obtained by selection of P4HB polymer as the material for forming a nerve guide.

The claims are definite to one of ordinary skill in the art who would understand the ordinary meaning of "suitable for".

The claims are not drawn to obvious variants of the Metabolix patent claims.

The rejections for double patenting over the claims in the Tepha patent applications are moot.

Allowance of claims 1 and 3-6 is respectfully solicited.

Respectfully submitted,

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Claims Appendix

1. (previously presented) A nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit tube or sheet suitable for nerve repair, the pores in the conduit having a diameter of between five and 500 microns, wherein the polymer comprises 4-hydroxybutyrate.
2. (cancelled)
3. (original) The device of claim 2 wherein the polymer is poly-4-hydroxybutyrate.
4. (original) The device of claim 1 wherein the pores of the conduits are greater than 5 μm in diameter.
5. (original) The device of claim 1, wherein the pores of the conduit are less than 500 μm in diameter.
6. (original) The device of claim 1 wherein the conduit comprises a material selected from the group consisting of nerve cells, growth factors, and drugs.
7. (withdrawn, previously presented) A method for preparing a nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit tube or sheet wherein the polymer comprises 4-hydroxybutyrate and wherein the device is prepared by thermally induced phase separation of the polymer in a solvent in combination with salt particles, removing the polymer solvent, and removing the salt particles to form pores between five and five hundred microns in diameter.
8. (withdrawn) The method of claim 7 comprising leaching with an alcohol followed by leaching with water or a solution comprising a surfactant.

9. (withdrawn) The method of claim 7 for preparing the device of claim 1 wherein the device is prepared by a combination of thermally induced phase separation and poragen leaching.

10. (withdrawn) The method of claim 8 wherein the surfactant is a polysorbate

11. (withdrawn, previously presented) A method of nerve repair or regeneration comprising providing a nerve regeneration device comprising 4-hydroxybutyrate polymer in the form of a wrapped porous conduit tube or sheet, the pores in the conduit having a diameter of between five and five hundred microns, wherein the diameter of the conduit is large enough so that it does not exert pressure on a regrowing nerve, but small enough to provide a good seal at the nerve.

12. (withdrawn) The method of claim 11 comprising inserting severed nerve ends into the conduit or wrapping the nerve ends with the polymer and sealing it into a conduit.

13. (withdrawn) The method of claim 12 wherein the device is sealed by application of heat.

14. (withdrawn) The method of claim 11 providing an axonal regeneration rate of at least 0.8 mm per day across a 10 mm sciatic nerve gap in an animal or human.

Evidence Appendix

Evidence Cited in the Application at page 2 and

Submitted with the Information Disclosure Statement filed on August 30, 2006.

PCT WO 88/06866 to Aebischer *et al.*

Hazari *et al.* in Vol. 24B *J. Hand Surgery*, pp. 291-295 (1999)

Ljungberg *et al.* in Vol.19 *Microsurgery*, pp. 259-264 (1999)

Hazari *et al.* in Vol. 52 *British J. Hand Surgery*, pp. 653-657 (1999)

PCT WO 03/041758 to Wiberg

PCT WO 01/54593

Related Proceedings Appendix

None